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(54) Title: NEW PROCESS 1

(57) Abstract: The invention refers to a process for the preparation of a self-dispersing or self-emulsifying tablet comprising the steps mixing a granulation medium containing an active lipophilic substance with one or more fillers and auxiliary components, granulation of said mixture into granules, drying of said granules, sieving of the granules into a homogeneous size, mixing of the granules with tableting aids, and compressing said mixture into tablets, which is characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid. The invention also refers to a process for the preparation of tablets from a granulation medium comprising oil and surfactant, as well as to tablets prepared by said processes.

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WO 03/061627 A1

NEW PROCESS 1

The present invention refers to a process for preparing self-dispersing or self-emulsifying tablets containing a lipophilic substance, as well as to tablets and granules obtained by said process.

BACKGROUND

Poorly soluble active drug substances most often present problems in the making of drug formulations. The water solubility is crucial for absorption and hence bioavailability in the case of the most important route of absorption, passive diffusion. In order to overcome a solubility problem, the formulator is compelled to either increase the solubility on the molecular level by creating a pro-drug or by adding solubility enhancing additives or excipients. The second alternative often includes excipients of lipophilic character like oils. In addition surface-active agents, or detergents are added in order to create an emulsion. The created emulsion could be thermodynamically stable, i.e. a microemulsion. Said formulations are mostly intended for use as wet systems as mixtures or soft gelatine capsules.

It is well known that lipophilic substances with a very low solubility in water will have a higher bioavailability when administered in a microemulsion, see for instance "Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects."

Constantinides, P. P. (1995) Pharmaceutical Research, 12, (11) 1561-1572; and "Enhanced intestinal absorption of an RGD peptide from water-in-oil microemulsions of different composition and particle size.", Constantinides, P.P. et al., (1995) Journal of controlled release 34, 109-116; and "Lipid-based vehicles for the oral delivery of poorly water soluble drugs", Humberstone, A.J. and Charman, W.N.; (1997) Advanced Drug Delivery Reviews, 25, 103-128.

Tablets are in general the preferred dosage form, being comparatively less expensive to manufacture, easy to store and administer. There is, however, no general way to formulate poorly soluble lipophilic drug substances as tablets with fast and high bioavailability.

PRIOR ART

A number of references are known referring to inclusion of a microemulsion in a solid dose form in order to replace costly and inconvenient capsule forms for administration of drugs with improved bioavailability.

Self-emulsifying tablets are disclosed by Schwarz, J., et al. in no. 6209 from the 27th Proceed. Int'l Symp. Control. Rel. Bioact. Mater. (2000) Controlled Release Society, Inc. A self-emulsifying controlled release tablet for oral delivery of hydrophobic drugs is described. The drug is contained within the oil droplets of the formed emulsion creating a significant improvement of in bioavailability. In a later article, no. 6107 from the 28th Proceed. Int'l Symp. Control. Rel. Bioact. Mater. (2001), Controlled Release Society, Inc., Schwartz, J., et al. describes a controlled release formulation that utilises the formation of a gel-forming matrix for creating a diffusion controlled release tablet.

WO 00/41676, Merck Sharpe and Dohme Ltd, discloses a self-emulsifying system for providing solid dosage forms of hydrophobic active agents, comprising a mixture of micro-crystalline cellulose with an oily substance, surfactant and water, which is extruded and spheronised into pellets. The pellets are said to be filled into capsules or to be compressed into tablets. There are, however, no examples of tablets nor any mentioning of tableting aids, and the described size distribution of the pellets does not seem to be suitable for tableting.

WO 00/09093, CIMA Labs Inc., discloses drug containing microemulsions adsorbed onto solid particles forming a free

flowing, compressible powder. Said powder can be converted into tablets, granules, pellets or other solid dosage forms.

WO 99/44589, Gattefossé S.A., discloses an oral pellet for immediate release of an active substance, comprising at least said active substance, a binding agent and a diluting agent.

There is, however, still a need of a process for production of self-dispersing or self-emulsifying immediate release tablets, wherein the total lipophilic content constitutes a substantial amount, in order to increase the solubility of a lipophilic active substance.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the dissolution in phosphate buffer, pH 7.4, of tablets according to the invention containing different amounts of curcumin compared to a curcumin tablet formulation without lipid and surfactant.

Figure 2 shows the dissolution in phosphate buffer, pH 7.4, of a tablet according to the invention containing cyclosporine-A in comparison to a Sandimmun Neoral® capsule.

DESCRIPTION OF THE INVENTION

It has now been found that a self-dispersing, immediate release tablet containing a lipophilic substance with low solubility in water can be prepared by a conventional tableting method, by using a granulation medium in the form of an emulsion, microemulsion or dispersed liquid crystalline phase. When the tablet is dissolved in water, or gastric juice or gastrointestinal fluids, a dispersion of the lipophilic substance is spontaneously formed.

Tablets are conventionally prepared by compressing a powder or granules or a mixture thereof. The most important properties of the powder and granules for manufacturing of tablets are flowability, compactability and homogeneity in order to produce tablets having a sufficient hardness, good weight control and good dose uniformity. Granulation is the process in which powder

particles are made to adhere to form larger particles i.e. granules. The granulation of powder together with optional binding material can be performed in several ways, such as wet, dry or melting processes. The distinct difference between wet and melt granulation is that wet granulation is followed by a drying step where the granulation medium, that is water or some other polar liquid, is dried off. Melt granulation on the other hand includes a cooling step where at least one of the melted materials solidifies.

The invention refers to a process for preparing a self-dispersing or self-emulsifying immediate release tablet, which is characterised by the following steps,

mixing a granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

granulation of said mixture into granules,

drying of said granules,

sieving of the granules into a size below 1 mm,

mixing of the granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.

The composition of the granulation medium is dependent on the process to be used, which in turn is dependent on the active substance to be dissolved or dispersed. Oil, surfactant and polar liquid can be mixed in different proportions and in different ways giving a microemulsion, an emulsion or micellar phase or a dispersed liquid crystalline phase.

The granulation medium can be an emulsion. An emulsion is a dispersion of one phase in another, such as oil in water, and the surfactants act as stabilisers of the emulsion. An emulsion is not thermodynamically stable and the formation thereof requires an energy input. A kinetically stable, finely dispersed emulsion can be obtained by agitation of the system and the

emulsion may remain finely dispersed for a relatively long time depending on the composition.

According to a preferred aspect the granulation medium is a microemulsion. Microemulsions are thermodynamically stable isotropically clear solutions consisting of water, oil and surfactants. They can be characterised as o/w (oil-in-water), w/o (water-in-oil) or as bicontinuous phases. According to another terminology they are described as a micellar or a reversed micellar solution. The formation of a microemulsion requires no energy input.

If water is replaced by another polar liquid, a non-aqueous microemulsion can be obtained.

According to still another aspect of the invention the granulation medium is a dispersed liquid crystalline phase. When oil, water and surfactants are mixed liquid crystalline phases can also be obtained, such as lamellar, hexagonal, reversed hexagonal and cubic liquid crystal phases. Just as with emulsions the liquid crystalline phases require a homogenisation before use.

Different phases of the three components oil, surfactant and polar liquids are described in for instance Jönsson et al. "Surfactants and Polymers in Aqueous Solutions", Wiley (1999). Evans and Wennerström "The Colloidal Domain, where physics, chemistry and biology meet", Wiley (1999).

The type of oil to be used in the process of the invention is determined by the solubility properties of the active substance. The use of oil/fat in tablet compositions imposes a binding reducing property that is dependent on the melting temperature, concentration of oil/fat and choice of other excipients. An oily component tends to break the interparticulate bondings and reduce the tablet strength and also increase capping and laminating tendencies of the compact. In order to reduce these problems and still enable a high concentration of oil/fat in the tablet formulation the choice of the melting point of the mixture of lipophilic active substance, oil and surfactant is

important, as well as the choice of binder, filler and tabletting aids.

The surfactant is preferably selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol.

The polar liquid can in addition to water be an alcohol, such as ethanol or propylene glycol.

The granulation can be performed in different ways using mixing or agitation equipment such as a planetary mixer, a high shear mixer or a fluid bed. Fluid bed has the advantage compared to the other techniques that the drying process can be performed in the same vessel as is used for the granulation. The other techniques normally require a discharging step between the granulation and drying if not a single processing equipment is used such as a vacuum/microwave high shear mixer. Granulation can also be performed by means of extrusion / spheronisation and spray drying, which, however, are more complex operations producing powder aggregates, which normally are not used for tablet production. To be suitable for tabletting the granules should preferably have an average diameter below 1 mm, especially within the range of 125-710 μm .

The choice of granulation medium and granulation process depends on the material to be granulated as well as the properties wanted for the granules. In some cases, specific properties of the active substance have to be considered when choosing granulation medium, method of granulation and tablet processing. The compression of the granules is typically done with low compressive force and with the addition of small amounts of plastic deformable binder.

A filler is by definition a component used for diluting the formulation in order to achieve a reasonable unit dose weight. In order to provide an immediate release tablet the filler must not form a gel, but should rather be of a non-swellable type. As examples of non-swellable fillers can be mentioned micro-

crystalline cellulose and dicalcium phosphate, which are not soluble, and lactose, which is soluble in water.

To achieve acceptable tableting properties when a high ratio of oil/fat is used, that is about $> 20\%$ of the tablet formulation, a binder typically has to be used. The binder is added to the granulation medium and hardens on drying to form solid bridges binding the particles together. As examples can be mentioned PVP (Povidone), cellulose derivatives, pre-gelatinised starch. The binder can be used dissolved in the granulation medium or as a dry powder in the final mix.

Tableting aids are for example lubricants, such as magnesium stearate, and disintegrants, such as croscarmellose sodium and sodium starch glycolate, and glidants, such as colloidal silicon dioxide (Aerosil 200). In addition flavouring, colouring, and coating agents can be added.

An active substance, preferably a pharmaceutically active substance, which preferably can be administered in a tablet according to the invention in order to improve the bioavailability, is for instance a hydrophobic or lipophilic substance with a low solubility in water. Substances having a log P value (octanol:water) of above 2 are candidates for the process of the invention.

The invention also refers to tablets prepared by the process.

Tablets can be manufactured as immediate release tablets but also with an enteric coating if the active substance is to be released in the intestines or if the active substance is susceptible to acidic degradation. Coatings can also be applied for taste-masking or to provide a special colour.

If large amounts of an active substance are to be administered it might be preferred to use another type of tablet, such as a lozenge, a chewable tablet or effervescent tablets.

When the tablet is brought into contact with water or gastric juice the molecularly dissolved active substance is spontaneously dispersed and a microemulsion, colloidal emulsion or drops of

emulsion are obtained, which will improve the distribution of the active substance. Disintegration of a lipid/surfactant containing tablet can result in for instance a microemulsion, an emulsion or fine colloidal emulsions, which all improve or facilitate the distribution of a lipophilic drug in the gastrointestinal tract.

According to another aspect the invention refers to a process for the preparation of a self-dispersing tablet comprising the following steps,

mixing a heated granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

granulation of said mixture into granules which are allowed to cool,

sieving of the granules into a size below 1 mm,

mixing of the granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

In said process the granulation medium consists of an oil/fat in combination with one or more surfactants, which are mixed with the lipophilic drug substance.

EXAMPLES

The following Examples 1-10 all refer to the preparation of granulation media. In Example 1 a microemulsion is obtained, in Examples 2-3 non-aqueous microemulsions, in Examples 4 an emulsion, and in Examples 5-6 dispersed liquid crystalline phases. In Example 7 the lipophilic substance curcumine is used as model of an active substance, and in Examples 8-10 the granulation media contains the lipophilic active substances naproxene, indomethacin and cyclosporine-A, respectively.

Examples 11-14 refer to wet granulation, Examples 15-18 to tableting using the granulation media described in Examples 1, 2, 7 and 10.

In the examples below the following substances are used as surfactants:

AKOLIP LM, Karlshamns AB, Sweden, a mixture of glycerolesters of C8-C18 fatty acids and macrogolesters of C8-C18 fatty acids (melting point 44°C, HLB-value 14);

AKOLINE HH, Karlshamns AB, glycerol esters of medium chain fatty acids (melting point 25°C, HLB-value 5-6);

AKOLINE MCM, Karlshamns AB, caprylic/capric glycerides (melting point 25°C, HLB-value 5-6);

Myrj 52s, Uniqema, Gouda, The Netherlands, PEG-40-stearate (HLB Value 16.9);

Rylo MG12, Danisco A/S, Copenhagen, Denmark;

Tween 80, Uniqema.

As example of an oil has been used:

AKOSOL 403, Karlshamns AB, hydrogenated palm kernel oil (melting point 34°C)

As polar liquids in addition to water has been used:

Ethanol 99.5 %;

PEG 600, polyethylene glycol (melting point 25°C);

PEG 3000, polyethylene glycol (melting point 48-54°C).

As examples of fillers have been used:

Avicel PH-102, FMC International, Ireland, microcrystalline cellulose;

Pharmatose DCL 11, DMV International, Holland, lactose; and

Isomalt DC-100, Palatinit, Germany, a mixture of disaccharides.

As an example of a binder has been used

Povidone K25, IFP, USA, polyvinyl pyrrolidone.

Example 1. Microemulsion

Akolip LM	9.0	%
Akosol 403	1.0	%
Water	90.0	%

Akolip LM and Akosol 403 are melted at 60°C and added to water at room temperature using gentle stirring. Oil soluble active

compounds can be dissolved in the surfactant/oil mixture before mixing with water or added to the microemulsion solution.

Example 2. Non-aqueous microemulsion

Akolip LM	72.0 %
Akoline MCM	13.5 %
Akosol 403	4.5 %
Ethanol 99.5 %	10.0 %

All components are added to ethanol, heated to about 40°C and stirred until a clear to slightly opalescent solution is obtained.

Example 3. Non-aqueous microemulsion

Akolip LM	7.0 %
Akoline HH	2.0 %
Akosol 403	1.0 %
Ethanol	90.0 %

Akolip LM, Akoline HH and Akosol 403 are melted at 60°C and added to ethanol at room temperature using gentle stirring. Oil soluble active compounds can be dissolved in the surfactant/oil mixture before mixing with ethanol or added to the microemulsion solution.

Example 4. Emulsion

Akolip LM	31.0 %
Akoline MCM	5.8 %
Akosol 403	2.0 %
PEG 3000	2.5 %
Ethanol 99.5 %	20.0 %
Water	38.7 %

The surfactants, Akolip LM and Akoline MCM, are melted to 60°C. The fat, Akosol 403, is separately melted to 60°C and added to the surfactants with gentle stirring. The PEG 3000 is added and allowed to melt in the mixture. Half of the water is added at 60°C and the resulting microemulsion is cooled to 30°C where the

ethanol and the rest of the water is added forming an oil-in-water emulsion, which can be used as a granulation medium.

Example 5. Liquid crystalline dispersion

Akolip LM	45.0	%
Akosol 403	5.0	%
Rylo MG12	10.0	%
Water	40.0	%

The solid components are melted at 60°C and carefully mixed by gentle stirring. Water is added using vigorous stirring to yield a semisolid, translucent, birefringent mass on cooling to 30°C. The liquid crystal formed in this way may be dispersed in additional water or in liquid oil or a melted fat to obtain a suitable granulation medium.

Example 6. Liquid crystalline dispersion

Akolip LM	15.0	%
Akosol 403	5.0	%
Rylo MG12	25.0	%
Water	55.0	%

The solid components are melted at 60°C and carefully mixed by gentle stirring. Water is added using vigorous stirring to yield a semisolid, translucent, birefringent mass on cooling to 30°C. The liquid crystal formed in this way may be dispersed in additional water or in liquid oil or a melted fat to obtain a suitable granulation medium. Oil soluble or sensitive actives as well as auxiliary ingredients can be added to the dispersion or even before performing the dispersion.

Example 7. Granulation medium containing curcumin as a model drug compound

Akolip LM	37.1	%
Akoline MCM	15.9	%
Curcumin	14.0	%
Ethanol, 99.5 %	33.0	%

The surfactants, Akolip LM and Akoline MCM, are melted and mixed at 60°C. The ethanol is added to the heated surfactant mixture during mixing. After cooling to 40°C, curcumin is added and the mixture is gently stirred until it is dissolved. The resulting liquid can be used as a granulation medium.

Example 8. Granulation medium containing naproxene

Akoline MCM	14.0 %
Tween 80	61.0 %
Naproxene	10.0 %
Ethanol 99.5%	15.0 %

The surfactants, Akoline MCM and Tween 80, are melted and mixed at 60°C. The ethanol is added to the heated surfactant mixture during mixing. After cooling to 40°C, naproxene is added and the mixture is gently stirred until it is dissolved. The resulting liquid can be used as a granulation medium.

Example 9. Granulation medium containing indomethacin

Akoline MCM	21.6 %
Tween 80	50.4 %
Indomethacin	8.0 %
Ethanol 99.5 %	20.0 %

The surfactants, Akoline MCM and Tween 80, are melted and mixed at 60°C. The ethanol is added to the heated surfactant mixture during mixing. After cooling to 40°C, indomethacin is added and the mixture is gently stirred until it is dissolved. The resulting liquid can be used as a granulation medium.

Example 10. Granulation medium containing cyclosporine-A

Akolip LM	35.0 %
Akoline MCM	15.0 %
Cyclosporine-A	16.7 %
Ethanol, 99.5 %	33.3 %

The surfactants, Akolip LM and Akoline MCM, are mixed in the pre-heated ethanol, 40°C. Cyclosporine-A is added and the

mixture is gently stirred until it is dissolved. The resulting liquid can be used as a granulation medium.

Example 11. Wet granulation process using a soluble filler

The granulation medium is prepared according to any of the Examples 1-10 and added to lactose or an equivalent filler. The amount of water in the granulation medium, if used, is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of about 20-60°C. The dry granules are passed through a sieve from approx. 500 to 1000 µm. The total amount of granulation medium depends on the composition of the medium. After drying a second granulation step could be performed.

The granulation medium from Example 7, at a temperature of about 40°C, is slowly added to Pharmatose DCL-11 in a high shear mixer in the following proportions:

Granulation medium 43 %

Lactose, Pharmatose DCL-11 57 %

The resulting granules are dried on trays at 30°C and passed through a 710-µm sieve. The dried and sieved granules are suitable for further tablet processing.

Example 12. Wet granulation process using soluble filler and binder

The granulation medium is prepared according to any of Examples 1-10 and added to lactose/Povidone. The Povidone could also be dissolved in the ethanol and included in the granulation medium. The amount of Povidone is optimised, from about 0.5 to 15 %. The amount of water in the granulation medium, if used, is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of about 20-60°C. The dry granules

are passed through a sieve from about 500 to 1000 μm . The total amount of granulation fluid depends on the composition of the fluid. After drying a second granulation step could be performed.

The granulation medium from Example 10, at a temperature of about 40°C is slowly added to a dry mix of Povidone and Isomalt DC-100 in a high shear mixer in the following proportions:

Granulation medium	48.4 %
Povidone K-25	6.4 %
Isomalt DC-100	45.2 %

The resulting granules are dried on trays at 30°C and passed through a 710- μm sieve. The dried and sieved granules are suitable for further tablet processing.

Example 13. Wet granulation process using insoluble filler

The granulation medium is prepared according to any of Examples 1-10 and added to microcrystalline cellulose, Avicel PH-102 or an equivalent filler. The amount of water (less critical compared to when a water-soluble filler is used) in the granulation medium, if used, is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 20-60°C. The dry granules are passed through a sieve from approx. 500 to 1000 μm . The total amount of granulation fluid depends on the composition of the fluid. After drying a second granulation step could be performed.

The granulation medium from Example 9 is used after cooling to approx. 40°C and slowly added to Avicel PH-102 in a high shear mixer in the following proportions:

Granulation medium	45.5 %
Avicel PH-102	54.5 %

The resulting granules are dried on trays at 30°C and passed through a 710- μm sieve. The dried and sieved granules are suitable for further tablet processing.

Example 14. Wet granulation process using insoluble filler and binder

The granulation medium is prepared according to any of Examples 1-10 and added to microcrystalline cellulose, Avicel PH-102 or an equivalent filler and Povidone. The Povidone could be dry mixed with the filler or dissolved in the granulation medium. The amount of Povidone is optimised, from approx. 0.5 to 15 %. The amount of water (less critical compared to when water-soluble filler is used) in the granulation medium, if used, is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 20-60°C. The dry granules are passed through a sieve from approx. 500 to 1000 µm. The total amount of granulation fluid depends on the composition of the fluid. After drying a second granulation step could be performed.

The granulation medium according to Example 10 is used and Povidone is dissolved in the medium. The resulting granulation medium, with a temperature of approx. 40°C is slowly added to Avicel PH-102 in a high shear mixer in the following proportions:

Granulation medium	55.0 %
Povidone K-25 dissolved in above	7.5 %
Avicel PH-102	37.5 %

The resulting granules are dried on trays at 30°C and passed through a 710-µm sieve. The dried and sieved granules are suitable for further tablet processing.

Example 15. Tablets originating from insoluble filler

The granulation medium was prepared according to Example 1 and added to Avicel PH-102 in the following proportions

Granulation medium	80 g
Avicel PH-102	200 g

The dried granules were passed through a 1.0 mm sieve and transferred to a Korsch PH 106 rotary tablet press equipped with round, diameter 10 mm punches. Tablets with a total weight of 400 mg and a crushing strength of 11-14 kp were produced.

Example 16. Tablets originating from soluble filler

The granulation medium was prepared according to Example 2 and added to Pharmatose DCL-11 in the following proportions

Granulation medium .	50 g
Pharmatose DCL-11	200 g

The dried granules were passed through a 1.0 mm sieve and transferred to a Korsch PH 106 rotary tablet press equipped with round, diameter 10 mm punches. Tablets with a total weight of 400 mg and a crushing strength of 6-8 kp were produced.

Example 17. Tablets with 5.2 % curcumin, originating from soluble filler and binder

The granulation medium was prepared according to Example 7 with the addition of Povidone, and added to Isomalt DC-100 in the following proportions

Granulation medium	
Akolip LM	56.0 g
Akoline MCM	23.0 g
Curcumin	21.0 g
Ethanol, 99.5 %	49.0 g

Binder

Povidone K-25	50.0 g
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Filler

Isomalt DC-100	250.0 g
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The ethanol is evaporated during the process. The dried granules were passed through a 1.0 mm sieve and transferred to a Diaf TM-20 single stroke tablet press equipped with round, diameter 12 mm punches. Tablets with a total weight of 565 mg and a crushing strength of 8.4 ± 0.4 kp ($n = 10$) were produced. The disintegration time was less than 15 min and the friability below 0.5 %.

The dissolution showed an increase in the solubility with increasing amount of model substance, up to 10.8 %. To be compared to the solubility of the tablet with the high concentration of model substance, 10.8 %, formulated without the self-emulsifying components (Fig. 1). The dissolution was performed using 500 ml phosphate buffer (pH 7.4) in a Prolabo Dissolutest with a paddle rate of 50 rpm and the temperature preset to 37°C.

Samples were withdrawn according to a certain time schedule and analysed with UV-spectrophotometry.

Example 18. Tablets with cyclosporine-A originating from soluble filler and binder

The granulation medium was prepared according to Example 10 with the addition of Povidone and added to Isomalt DC-100 in the following proportions

Granulation medium

Akolip LM	23.0 g
Akoline MCM	10.0 g
Cyclosporine-A	11.0 g
Ethanol, 99.5 %	22.0 g

Binder

Povidone K-25	22.0 g
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Filler

Isomalt DC-100	154.0 g
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The ethanol was evaporated during the process. The dried granules were passed through a 1.0 mm sieve and transferred to a Diaf TM-20 single stroke tablet press equipped with round, diameter 12 mm punches. Tablets with a total weight of 500 mg (giving a final concentration of 25 mg Cyclosporine-A per tablet) and a crushing strength between 6 and 8 kp were produced. The dissolution from the produced tablets was determined and compared to a Sandimmun Neoral® 25 mg capsule (Fig. 2). The dissolution was found to be slightly faster and cyclosporine-A was solved to the same extent as the commercial

capsule formulation. The dissolution was performed using phosphate buffer (pH 7.4) in a Prolabo Dissolutest with a paddle rate of 50 rpm and the temperature preset to 37°C.

Samples were withdrawn according to a certain time schedule and analysed with reversed phase HPLC.

CLAIMS

1. A process for the preparation of a self-dispersing or self-emulsifying immediate release tablet comprising the following steps,

 mixing a granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

 granulation of said mixture into granules,

 drying of said granules,

 sieving of the granules into a size below 1 mm,

 mixing of the granules with tableting aids, and

 compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.

2. A process according to claim 1, characterised in that the granulation medium is a microemulsion.

3. A process according to claim 1, characterised in that the granulation medium is an emulsion.

4. A process according to claim 1, characterised in that the granulation medium is a liquid crystalline phase.

5. A process for the preparation of a self-dispersing immediate release tablet comprising the following steps,

 mixing a heated granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

 granulation of said mixture into granules which are allowed to cool,

 sieving of the granules into a size below 1 mm,

 mixing of the granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

6. A process according to any of claims 1-5, characterised in that the surfactant is selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol.

7. A tablet, characterised in being prepared by a process according to any of claims 1-6.

FIGURE 1

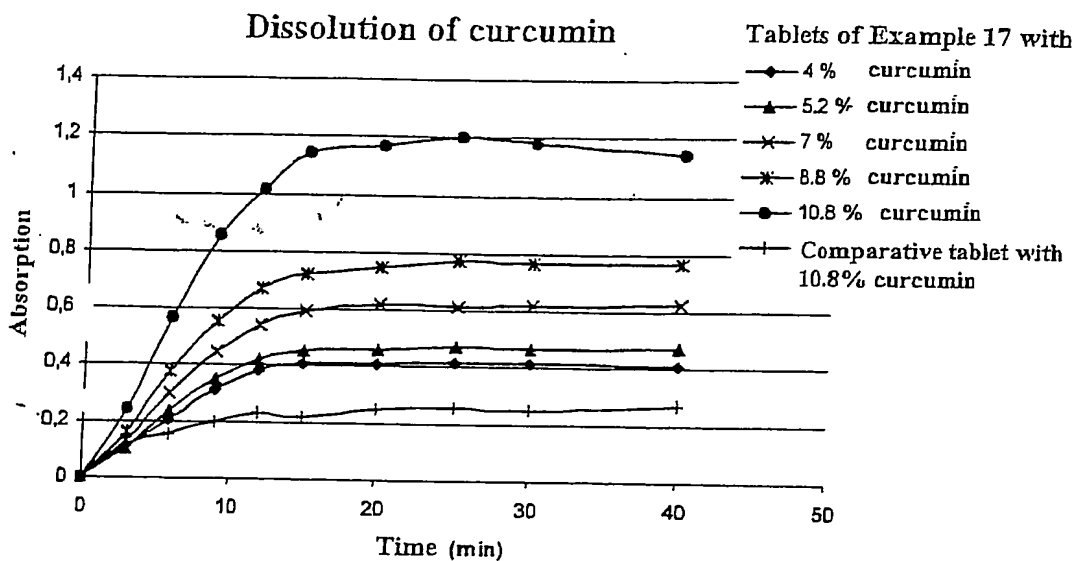
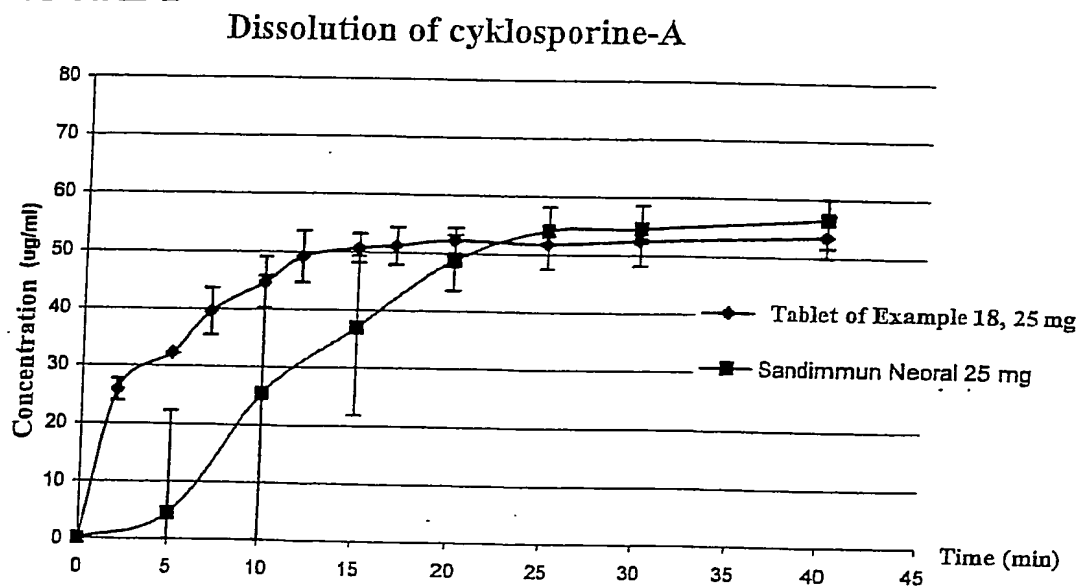


FIGURE 2



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